

## RESEARCH

# Prognostic utility of blood pressure-adjusted global and basal systolic longitudinal strain

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## Abstract

Assessment of global longitudinal systolic strain (GLS) and longitudinal systolic strain of the basal segments (BLS) has shown prognostic value in cardiac disorders. However, strain is reduced with increased afterload. We assessed the prognostic value of GLS and BLS adjusted for afterload. GLS and BLS were determined in 272 subjects with normal ejection fraction and no known coronary disease, or significant valve disease. Systolic blood pressure (SP) and diastolic blood pressure (DP) obtained at the time of echocardiography were used to adjust GLS and BLS as follows: strain  $\times$  SP (mmHg)/120 mmHg and strain  $\times$  DP (mmHg)/80 mmHg. Patients were followed for cardiac events and mortality. The mean age was  $53 \pm 15$  years and 53% had hypertension. There were 19 cardiac events and 70 deaths over a mean follow-up of  $26 \pm 14$  months. Cox analysis showed that left ventricular mass index ( $P=0.001$ ), BLS ( $P<0.001$ ), and DP-adjusted BLS ( $P<0.001$ ) were independent predictors of cardiac events. DP-adjusted BLS added incremental value ( $P<0.001$ ) to the other two predictors and had an area under the curve of 0.838 for events. DP ( $P=0.001$ ), age ( $P=0.001$ ), ACE inhibitor use ( $P=0.017$ ), and SP-adjusted BLS ( $P=0.012$ ) were independent predictors of mortality. SP-adjusted BLS added incremental value ( $P=0.014$ ) to the other independent predictors. In conclusion, DP-adjusted BLS and SP-adjusted BLS were independent predictors of cardiac events and mortality, respectively. Blood pressure-adjusted strain added incremental prognostic value to other predictors of outcome.

## Key Words

- ▶ global systolic longitudinal strain
- ▶ basal systolic longitudinal strain
- ▶ afterload
- ▶ blood pressure
- ▶ 2D speckle-tracking echocardiography

## Introduction

Assessment of global longitudinal systolic strain (GLS) and basal longitudinal systolic strain (BLS) have shown utility for prediction of prognosis in various cardiac disorders (1, 2, 3, 4). In some studies, longitudinal strain has been shown to be a more sensitive indicator of left ventricular (LV) systolic dysfunction than traditional measures of function (5, 6). The detection of early abnormalities in myocardial function by strain assessment likely

accounts for the superior ability of the technique to predict outcome in some cardiac disorders (3, 4, 7). However, longitudinal strain is similar to many other measures of systolic function in that it is influenced by loading conditions (8, 9). Both experimental and clinical studies have shown that increased afterload reduces longitudinal strain. The early improvement in longitudinal strain occurring in patients with aortic stenosis undergoing valve

replacement has been attributed to marked reductions in afterload (10, 11, 12). The results of these studies suggest that depression of longitudinal strain at times can be a temporary change reflective of afterload mismatch rather than irreversible myocardial injury. This known effect of afterload on strain suggests that adjustment of GLS and BLS for afterload might improve the diagnostic and prognostic accuracy of strain assessment. In this retrospective test-of-concept study, the prognostic value of longitudinal strain adjusted for afterload was investigated using blood pressure (BP) as a simple measure of afterload.

## Methods

### Study population

The study was approved by the Indiana University Institutional Review Board. From 20 January 2010 to 9 May 2011, 780 patients had speckle tracking assessment of LV strain. Four hundred forty-two patients with reduced ejection fraction (<50%), significant valve disease, and known coronary artery disease were excluded. Of the remaining 338 subjects, 28 (8.3%) were excluded because of inadequate quality strain studies, 9 (2.7%) because of lack of follow-up, and 29 (8.6%) because of no BP recordings, leaving 272 patients in the study group.

### 2D echocardiography

The echocardiographic examinations and standard 2D measurements were performed according to published guidelines (13). Vivid 7 and Vivid Q echocardiographs (General Electric Medical Systems, Milwaukee, WI, USA) equipped with M4S transducers were used to acquire images at 50–70 frames/s. The images were digitally stored and measurements were performed by trained sonographers. Wall stress was calculated in a subset of patients (14).

### Speckle tracking analysis

Images were acquired in three apical views (long-axis, four-chamber, and two-chamber). Strain analysis was performed by a trained sonographer using propriety software on the echocardiograph. The operator identified three points on each view (the two borders of the mitral annulus and the apex). The software then determined peak systolic longitudinal strain in six segments of each view along with defining aortic valve closure. GLS was calculated based on the average strain for each of the three views (17 segments with 6 basal, 6 mid, 4 apical, and the apex). BLS was calculated by averaging strain values of the six basal segments.

### BP-adjusted strain

Systolic blood pressure (SP) and diastolic blood pressure (DP) were recorded at the time of each echocardiographic exam. GLS and BLS were indexed to SP and DP using the population-based average BP of 120/80 mmHg. Based on previous studies documenting an inverse relationship of afterload and strain, GLS and BLS were adjusted for SP and DP as follows: systolic pressure-adjusted GLS (SPGLS) =  $GLS \times SP/120$ . We hypothesized that higher SP at the time of strain assessment may result in lower strain values, so strain was adjusted higher using the ratio of SP and 120 mmHg. Conversely, we assumed that SP < 120 mmHg at the time of strain assessment may result in higher strain values, so strain was adjusted lower by a factor of SP/120. SP-adjusted BLS (SPBLS) was derived for each patient in a similar fashion. GLS and BLS were also adjusted for DP. DP-adjusted GLS (DPGLS) =  $GLS \times DP/80$  and DP-adjusted BLS (DPBLS) =  $BLS \times DP/80$ .

### Follow-up

Retrospective follow-up was conducted by review of medical records, death, and obituary indices. Study end points were all-cause mortality and cardiac events defined as heart failure, nonfatal infarction, or cardiac death. Heart failure was defined as admission for heart failure with typical exam and chest X-ray findings and elevated brain natriuretic peptide. Infarction was considered present based on typical symptoms, electrocardiogram findings, and enzyme elevation. Cardiac death was defined as death due to intractable heart failure, infarction, or sudden death without an obvious noncardiac cause.

### Statistical methods

Analysis was performed using SPSS (version 21.0). Cox regression was used to determine univariate predictors of cardiac events and mortality with variables having  $P < 0.05$  considered as significant. Multivariate analysis was conducted using variables with  $P < 0.10$  on univariate analysis. To determine if BP-adjusted strain provided incremental prognostic value, step-wise Cox analysis was performed by entering all multivariate predictors in the first step and BP-adjusted predictors in a second step. Survival was assessed using the Kaplan–Meier method and the log rank test. Receiver operator characteristic (ROC) curve analysis was conducted to determine the accuracy of BP-adjusted strain for prediction of events or mortality. Linear regression analysis was performed in the first 101

**Table 1** Clinical and echocardiographic variables.

Characteristic	n=272
Age (years)	53±15
Women	50%
Dyslipidemia	25%
Smoker	35%
Hypertension	53%
Diabetes mellitus	9.6%
ACE inhibitor	25%
β-blocker	32%
HMG-CoA reductase inhibitor	23%
SP (mmHg)	125±20
DP (mmHg)	73±12
BSA (m <sup>2</sup> )	1.9±0.3
LV mass index (g/m <sup>2</sup> )	89±30
Ejection fraction (%)	63±6
GLS	-18.9±3.7
BLS	-17.2±3.9
SPGLS (%)	-19.6±4.4
DPGLS (%)	-17.0±3.9
SPBLS (%)	-17.8±4.1
DPBLS (%)	-15.5±3.7

BLS, basal longitudinal systolic strain; BSA, body surface area; DP, diastolic blood pressure; DPBLS, diastolic blood pressure-adjusted basal longitudinal strain; GLS, global longitudinal systolic strain; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LV, left ventricular; SP, systolic blood pressure; SPBLS, systolic blood pressure-adjusted basal longitudinal strain.

subjects enrolled in the study to determine the relationship of SP, DP, and wall stress with GLS and BLS. Steiger's Z-test was used to compare correlation coefficients.

## Results

### Study population

Clinical characteristics of the study group are shown in [Table 1](#). The indications for echocardiography in the 272 subjects were: evaluation of symptoms in 70 (25.7%), evaluation before noncardiac surgery in 84 (30.9%), LV function assessment before chemotherapy in 66 (24.3%), evaluation for suspected coronary artery disease in 29 (10.7%), and miscellaneous indications in 23 (8.4%) subjects. SP ranged from 81 to 190 mmHg and DP from 38 to 120 mmHg.

### Outcome

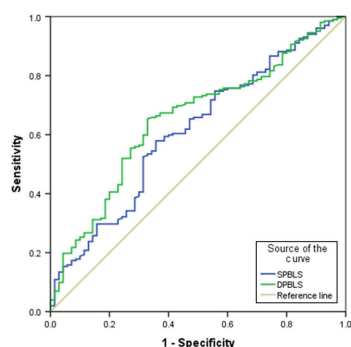
There were 70 deaths over a mean follow-up of 26±14 months. The results of univariate and multivariate Cox analysis for mortality are shown in [Table 2](#). Lower DP,

**Table 2** Univariate and multivariate predictors of mortality.

Variables	Survived (n=202)	Died (n=70)	Univariate			Multivariate <sup>†</sup>		
			HR	95% CI	P	HR	95% CI	P <sup>‡</sup>
Age (year)	52±15	57±14	1.02	1.00–1.04	0.014	1.03	1.01–1.05	0.001
Women	102 (50%)	33 (47%)	0.83	0.52–1.33	0.433			
Hypertension	109 (54%)	35 (50%)	0.80	0.50–1.28	0.359			
Hyperlipidemia	54 (27%)	13 (19%)	0.62	0.34–1.14	0.126			
Smoking	66 (33%)	29 (41%)	1.36	0.84–2.18	0.208			
Diabetes mellitus	19 (9.4%)	7 (10%)	1.07	0.49–2.34	0.866			
ACE inhibitor	56 (28%)	11 (16%)	0.48	0.25–0.91	0.025	0.44	0.22–0.86	0.017
β-blocker	62 (31%)	24 (34%)	1.09	0.67–1.79	0.726			
Statin	51 (25%)	11 (16%)	0.55	0.29–1.06	0.073			0.256
SP (mmHg)	128±19	119±20	0.98	0.97–0.99	0.002			0.962
DP (mmHg)	74±11	68±12	0.95	0.93–0.98	<0.001	0.96	0.94–0.98	0.001
BSA (m <sup>2</sup> )	1.9±0.3	1.9±0.3	0.86	0.36–2.06	0.738			
LA-AP diameter (cm)	3.9±0.7	3.8±0.6	0.99	0.71–1.38	0.960			
LVDD base (cm)	4.3±0.6	4.3±0.7	0.94	0.66–1.34	0.733			
LV mass index (g/m <sup>2</sup> )	88±29	91±33	1.00	1.00–1.01	0.522			
EF (%)	63±6	63±6	1.01	0.97–1.05	0.546			
GLS (%)	-18.9±3.8	-18.8±3.5	1.00	0.94–1.07	0.998			
BLS (%)	-17.3±3.8	-16.8±4.1	0.98	0.92–1.04	0.540			
SPGLS (%)	-20.0±4.4	-18.5±4.1	0.94	0.89–0.99	0.028			0.342
DPGLS (%)	-17.5±3.9	-15.8±3.5	0.91	0.86–0.97	0.002			0.424
SPBLS (%)	-18.2±4.0	-16.5±4.2	0.93	0.88–0.98	0.007	0.93	0.88–0.98	0.012
DPBLS (%)	-16.0±3.6	-14.0±3.6	0.90	0.84–0.95	<0.001			0.769

<sup>†</sup>Multivariate analysis using univariate predictors with  $P<0.10$  as candidate variables. <sup>‡</sup>Multivariate significance defined as  $P<0.05$ . Candidate variables not included in final model have  $P$ -value only listed.

BLS, basal longitudinal systolic strain; BSA, body surface area; DP, diastolic blood pressure; DPBLS, diastolic blood pressure-adjusted basal longitudinal strain; GLS, global longitudinal systolic strain; LA-AP, left atrial anterior-posterior; LVDD, left ventricle diastolic diameter; SP, systolic blood pressure; SPBLS, systolic blood pressure-adjusted basal longitudinal strain.

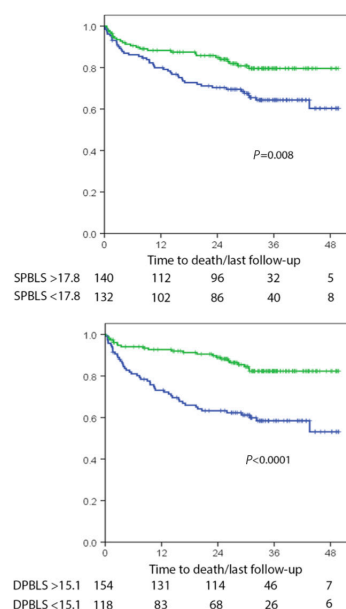


**Figure 1**

ROC curve for DPBLS and SPBLS as predictors of mortality. For DPBLS, the AUC was 0.651 with optimal threshold value of 15.1, sensitivity of 0.653, and specificity of 0.671. For SPBLS, the AUC was 0.610 with threshold value of 17.8, sensitivity of 0.579, and specificity of 0.643. DPBLS, diastolic blood pressure-adjusted basal longitudinal strain; SPBLS, systolic blood pressure-adjusted basal longitudinal strain.

lower SP, lack of statin use, lack of ACE inhibitor use, higher age, and all BP-adjusted strain measures were univariate predictors. Lower SPBLS, lower DP, increased age, and lack of ACE inhibitor use were independent predictors of mortality. Step-wise analysis showed that SPBLS added incremental prognostic value to the combination of ACE inhibitor use, age, and DP (Chi-square increase from 27.4 to 34.3 ( $P=0.014$ )). The results of ROC analysis using DPBLS and SPBLS are shown in Fig. 1. The area under the curve (AUC) was 0.651 for DPBLS and 0.610 for SPBLS. Survival curves for SPBLS and DPBLS are shown in Fig. 2 using the threshold values defined by ROC analysis. Survival was better for subjects with DPBLS  $>15.1$  and SPBLS  $>17.8$ . To determine if the diagnostic value of adjustment of BLS for mortality was dependent on the extent of deviation of SP from the reference value of 120 mmHg, the population was divided into two groups. Group 1 comprised 50% of subjects with the highest and lowest SPs and the remaining 50% (group 2) comprised those in the middle range of SPs (112–138 mmHg). The AUC in group 1 was 0.661 vs 0.506 in group 2 ( $P=0.06$ ), suggesting that BP adjustment of BLS was most important in those with the greatest deviation of SP.

There were 19 patients with cardiac events, 10 patients had heart failure, and 13 patients had cardiac death. The results of Cox analysis for events are shown in Table 3. Lack of  $\beta$ -blocker use, higher left atrial diameter, higher LV mass index, lower DP, lower SP, lower BLS, and lower values of all BP-adjusted strain measures were univariate predictors. Lower DPBLS, BLS, and higher LV mass index were independent predictors of events. Step-wise analysis showed that DPBLS added incremental value to the combination of LV mass index and BLS (Chi-square



**Figure 2**

Kaplan–Meier curves of overall survival. Patients stratified by ROC optimal thresholds for SPBLS (top) and DPBLS (bottom). DPBLS, diastolic blood pressure-adjusted basal longitudinal strain; SPBLS, systolic blood pressure-adjusted basal longitudinal strain.

increase from 17.9 to 46.2 ( $P<0.001$ ). The results of ROC analysis using DPBLS and SPBLS are shown in Fig. 3. The AUC was 0.838 for DPBLS and 0.770 for SPBLS. Survival curves for events are shown in Fig. 4 using the threshold values defined by ROC analysis. Cardiac event-free survival was better in subjects with DPBLS  $>14.1$  and SPBLS  $>14.9$ .

### Correlation of BP, wall stress, GLS, and BLS

SP and DP were inversely correlated with GLS: SP vs GLS ( $r=-0.26$ ,  $P=0.009$ ); DP vs GLS ( $r=-0.33$ ,  $P=0.001$ ) (Fig. 5). SP and DP were also inversely correlated with BLS (Fig. 6), with slightly but not significantly stronger correlation coefficients compared with the relationship of BP with GLS: SP vs BLS ( $r=-0.32$ ,  $P=0.001$ ); DP vs BLS ( $r=-0.44$ ,  $P<0.001$ ). Wall stress was inversely correlated with GLS: wall stress vs GLS ( $r=-0.25$ ,  $P=0.013$ ). An inverse correlation of wall stress and BLS was not significant ( $r=-0.17$ ,  $P=0.087$ ). Steiger's Z-test showed significantly better correlation between DP and BLS than between wall stress and BLS ( $P=0.017$ ).

### Discussion

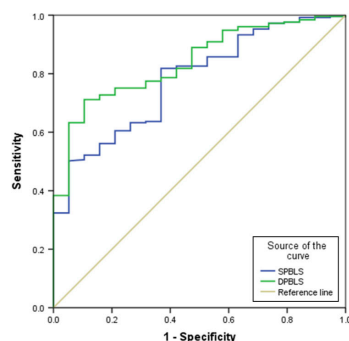
The results of our study showed that BP-adjusted measures of longitudinal systolic strain were independent

**Table 3** Univariate and multivariate predictors of cardiac events.

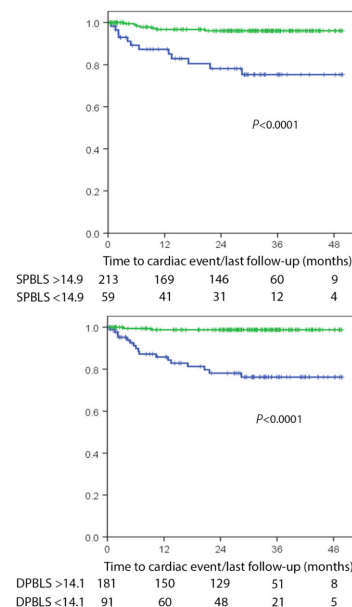
Variables	Nonevent (n=253)	Event (n=19)	Univariate			Multivariate <sup>†</sup>		
			HR	95% CI	P	HR	95% CI	P <sup>‡</sup>
Age (year)	53±15	56±14	1.02	0.98–1.05	0.322			
Women	127 (50%)	8 (42%)	0.68	0.27–1.68	0.400			
Hypertension	132 (52%)	13 (68%)	1.78	0.68–46.9	0.241			
Hyperlipidemia	60 (24%)	7 (37%)	1.66	0.65–4.21	0.288			
Smoking	85 (34%)	10 (53%)	2.18	0.89–5.36	0.090			0.855
Diabetes mellitus	23 (9.1%)	3 (15.8%)	1.85	0.54–6.34	0.330			
ACE inhibitor	63 (25%)	4 (20%)	0.69	0.23–2.08	0.512			
β-blocker	75 (30%)	11 (48%)	2.92	1.17–7.25	0.021			0.384
Statin	55 (22%)	7 (37%)	1.81	0.71–4.60	0.212			
SP (mmHg)	126±19	113±22	0.96	0.93–0.98	0.002			0.217
DP (mmHg)	74±12	63±14	0.91	0.87–0.95	<0.001			0.837
BSA (m <sup>2</sup> )	1.9±0.3	2.0±0.3	1.83	0.35–9.62	0.474			
LA-AP diameter (cm)	3.8±0.7	4.3±0.7	2.07	1.31–3.28	0.002			0.050
LVDD base (cm)	4.3±0.6	4.5±0.8	1.56	0.73–3.31	0.248			
LV mass index (g/m <sup>2</sup> )	87±26	114±56	1.02	1.01–1.03	<0.001	1.02	1.01–1.03	0.001
EF (%)	63±6	61±7	0.95	0.88–1.03	0.241			
GLS (%)	−19.0±3.6	−17.5±4.8	0.91	0.81–1.02	0.094			0.588
BLS (%)	−17.4±3.7	−15.0±5.0	0.87	0.78–0.97	0.011	1.49	1.24–1.78	<0.001
SPGLS (%)	−19.8±4.3	−16.2±4.5	0.83	0.75–0.92	<0.001			0.294
DPGLS (%)	−17.3±3.7	−13.3±3.5	0.77	0.68–0.86	<0.001			0.519
SPBLS (%)	−18.1±4.0	−13.7±4.0	0.80	0.73–0.88	<0.001			0.418
DPBLS (%)	−15.8±3.6	−11.2±3.0	0.75	0.67–0.83	<0.001	0.49	0.38–0.64	<0.001

BLS, basal longitudinal systolic strain; BSA, body surface area; DP, diastolic blood pressure; DPBLS, diastolic blood pressure-adjusted basal longitudinal strain; GLS, global longitudinal systolic strain; LA-AP, left atrial anterior-posterior; LVDD, left ventricle diastolic diameter; SP, systolic blood pressure; SPBLS, systolic blood pressure-adjusted basal longitudinal strain.

predictors of both cardiac events and mortality. SPBLS added incremental prognostic value for prediction of mortality and DPBLS added incremental value for prediction of events. The accuracy of BP-adjusted strain for prediction of mortality was fair, but both SPBLS and DPBLS yielded excellent accuracy for prediction of

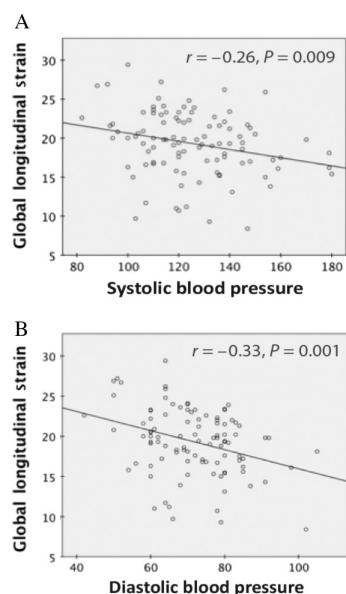


**Figure 3** ROC curve for SPBLS and DPBLS as predictors of cardiac events. For DPBLS, the AUC was 0.838 with optimal threshold value of 14.1, sensitivity of 0.711, and specificity of 0.895. For SPBLS, the AUC was 0.778 with optimal threshold value of 14.9, sensitivity of 0.818, and specificity of 0.632. DPBLS, diastolic blood pressure-adjusted basal longitudinal strain; SPBLS, systolic blood pressure-adjusted basal longitudinal strain.



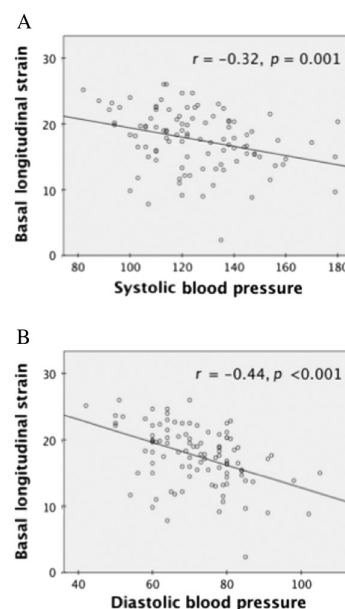
**Figure 4** Kaplan–Meier curves of for event-free follow-up. Patients stratified by ROC optimal thresholds for SPBLS (top) and DPBLS (bottom). DPBLS, diastolic blood pressure-adjusted basal longitudinal strain; SPBLS, systolic blood pressure-adjusted basal longitudinal strain.





**Figure 5**

Regression curves depicting the correlation between global longitudinal strain and (A) systolic blood pressure; (B) diastolic blood pressure.



**Figure 6**

Regression curves depicting the correlation between basal longitudinal strain and (A) systolic blood pressure; (B) diastolic blood pressure.

events. Unadjusted BLS was predictive of events, but unadjusted strain was not predictive of mortality.

Assessment of longitudinal strain is gaining popularity as a method to detect early cardiac disease and to predict outcome in disorders such as diabetes, hypertension, coronary disease, cardiomyopathy, and the use of cardiotoxic agents. Along with various disorders that can directly affect myocardial contractility and longitudinal deformation, it is apparent that loading conditions can directly affect the marker that we are using as a measure of myocardial function. Animal studies have shown that increased afterload reduces longitudinal strain (9, 15, 16). In a mouse model, Bauer and coworkers have shown that BLS is more affected by afterload than GLS or apical longitudinal strain (16). Human studies have also shown that increases in afterload are associated with reductions in strain (8, 17, 18). Several studies have shown a rapid, partial improvement of strain after valve replacement for aortic stenosis, which has been attributed to reduction of afterload (10, 11, 12, 19, 20).

To our knowledge, there are limited data on the clinical value of adjustment of strain for loading conditions. The results of our study suggest that adjustment of GLS and BLS for afterload can significantly affect the clinical utility of these measures in certain populations. Our study included subjects with a lower likelihood of significant myocardial disease. In this population,

afterload may have had a relatively larger influence on GLS and BLS compared with a population with a higher prevalence or greater severity of myocardial disease in which strain would be more affected by myocardial contractile abnormalities.

We chose to adjust GLS and BLS for afterload based on BP because it was readily available and easily measured. It could be argued that adjustment of GLS and BLS should be made with a more sophisticated or comprehensive measure of afterload such as wall stress that takes into account both peripheral loading conditions and cardiac structure. However, in our study, both SP and DP had significant inverse correlations with strain, whereas wall stress had a modest inverse correlation with GLS and an insignificant inverse correlation with BLS. These data suggest that for the purpose of adjustment of strain, the use of BP may be sufficient. Various studies have reported a nonsignificant to highly significant relationship between wall stress and longitudinal systolic function. In normal subjects, Hurlburt and coworkers (18) found a weak inverse relationship between longitudinal strain and wall stress ( $r = -0.11$ ,  $P < 0.05$ ), whereas Donal and coworkers (9) found a strong inverse relationship between longitudinal strain and wall stress ( $r = -0.68$ ,  $P < 0.005$ ). In hypertensives, Aurigemma and coworkers (21) found no relationship between longitudinal shortening and wall stress.

Previous clinical studies have documented an association between BP and strain. A meta-analysis of studies reporting normal values of GLS found a wide range (−15.9 to −22.1% mean, −19.7%; 95% CI −20.4 to −18.9%) (22). Variations in normal values of GLS were associated with differences in SP, but not with gender, age, or frame rate. The authors concluded that SP should be considered in the interpretation of strain values. Using handgrip exercise in healthy volunteers, Weiner and coworkers (8) showed that longitudinal strain declined an average of 12%, with an average increase in SP of 35 mmHg and DP of 27 mmHg. With handgrip, the mean value of GLS was −18.2% suggesting that some patients could have been classified as having abnormal ventricular contraction solely due to increased afterload. Our study included subjects with a wide range of SP (81–190 mmHg) and DP (38–120 mmHg), indicating in some individuals there were substantial adjustments in strain based on BP recordings. Our data indicate that BP adjustment of strain has the greatest value in those with the largest deviations of systolic BP from the normal-reference value.

GLS has been shown to have both diagnostic and prognostic utility in various disorders, but recent reports have shown that the clinical value of BLS may exceed that of GLS. In clinical studies, changes in BLS appear to be a greater predictor of subsequent disease in amyloidosis as well as predicting symptoms in aortic stenosis and differentiating hypertensive from nonhypertensive individuals (3, 23, 24, 25, 26, 27). The results of our study showed that adjustment of BLS for afterload may have greater clinical impact than adjustment of GLS for BP. The effects of afterload have been found to be highest at the base of the LV (25). The relative delay in contraction of basal vs apical segments may also contribute to disproportionate loading of basal segments (26, 28).

## Limitations

The limitations of our study include the retrospective design and heterogeneous subject population. The effect of adjustment of strain for BP may be less in a population with a higher prevalence of cardiac disease, in which strain values may be more affected by the disease state rather than loading conditions. A modest number of subjects (8.3%) were excluded because of technically inadequate strain studies. We chose a population-based average BP of 120/80 mmHg to serve as the standard for adjustment of afterload. This standard may or may not

be appropriate for other populations. We also did not validate threshold values of BP-adjusted strain that were found to be useful in this study in a separate population. Additional, prospective studies are needed to define the prognostic value of BP-adjusted strain.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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